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MUMMERT, STEPHANIE KANE				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

seapatentdocket@dw.com

Office Action Summary

Application No.

10/581,224

Applicant(s)

DAY ET AL.

Examiner

STEPHANIE K. MUMMERT

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 December 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 7/31/08
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I and the species of Histone H4, SEQ ID NO:36, SEQ ID NO:130-131 and detection via methylation specific primers, in the reply filed on December 6, 2010 is acknowledged.

Claims 11-13, 19-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 6, 2010.

Claims 1-11, 12-18, 27-37 are pending and will be examined.

Claim Interpretation

The terms referring to "target nucleic acids comprising essentially of all or part of the sequence of a gene or a genomic sequence.... comprise at least one CpG dinucleotide sequence" (see claim 1) are being given the broadest reasonable interpretation in light of the specification. While Applicant may intend for the at least one CpG dinucleotide to be detected in the context of the sequence as claimed, as currently recited, the claim reads on any CpG dinucleotide with any degree of complementarity to the claimed genes or specific sequences. Therefore, the claims will be given the broadest reasonable interpretation in a broad anticipation rejection. Similar rejections will be made, where appropriate, in a broad obviousness rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-10, 14-18 and 28-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Legal Analysis

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

These claims are directed to detection of prostate cancer cell proliferative disorders using nucleic acid sequences which "distinguishes between methylated and non-methylated CpG dinucleotides" comprising "at least one CpG dinucleotide". The claims are also directed to detection of sequences which comprise SEQ ID NO:130, 131 or a complement thereof, sequences which comprise at least one CpG dinucleotide of SEQ ID NO:36 or SEQ ID NO:1023. Therefore, the claims encompass a genus of nucleic acids that comprise sequences capable of binding to SEQ ID NO:36, 130, 131 and 1023. There are no limitations or instructions provided

regarding the minimum number of complementary nucleic acids which meet the limitation of "reagents that distinguishes between methylated and non-methylated CpG dinucleotides" and which comprise at least one CpG dinucleotide. There are also no limitations or instructions regarding the minimum number of complementary nucleic acids which meet the limitation of "complementary to, or hybridizes under modestly stringent conditions". As currently disclosed and recited, the term may read on as little as two consecutive nucleotides and as many as the full length sequences of the individual sequences. Not only are there no structural limitations or requirements which provide guidance on the identification of nucleic acids related to SEQ ID NO: 36, 130, 131 and 1023, but there are no functional limitations in the claim either. Thus, these claims fail on both prongs of the written description analysis since there is no function for the broad structures to define. Furthermore, the claims encompass a genus of nucleic acids that comprise sequences which are "complements thereof" which comprise variants or complements of sequences comprising SEQ ID NO:36, 130, 131 and 1023 which have not been defined.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

"A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

This is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the specific SEQ ID NO: 36, 130, 131 and 1023 is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim.

Absence of a representative number of species

In the current case, the first question is what constitutes a generic claim. The genus of nucleic acids includes any nucleic acid with any degree of homology across the entire nucleic acid sequence of SEQ ID NO:36, 130, 131 and 1023 including nucleic acids with as few as 2, 4, 8, 12, or 24 for example, contiguous nucleotides homologous to SEQ ID NO:36, 130, 131 and 1023, or to nucleic acids which comprise ‘a complement thereof’ of nucleic acids which represent allelic variants of SEQ ID NO:36, 130, 131 and 1023. Thus, the claim reads on a multitude of nucleic acids, including sequences which themselves may not yet be described in the scientific literature. In order to provide a representative number of species, in a genus which contains literally hundreds of billions of different members, the court in Lilly required “A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. (Lilly at page 1406).” Lilly continues to note that in other cases, two chemical compounds in a subgenus were insufficient to describe that genus. In the current case, only four species are disclosed, SEQ ID NO:36, 130, 131 and 1023. These species represent a specific nucleic acid sequence and are not representative of the entire genus.

Absence of any structure-function relationship

The second issue is whether there is any structure function relationship which correlates a function with a particular structure. This question fundamentally addresses the issue of whether there is any structure which the specification demonstrates is necessarily correlated with the primer or probe functions of the nucleic acid of SEQ ID NO:36, 130, 131 and 1023. In this case, the answer is no, there is no structure given, other than SEQ ID NO:36, 130, 131 and 1023.

Since there is no common structure among the nucleic acids that are specifically associated with the unknown function of the nucleic acid, except for roles for the oligonucleotides as primers or probes, there is no structure-function relationship between the multiple broad genres of nucleic acids claimed.

The claim scope broadly encompasses any nucleotide sequence capable of binding to SEQ ID NO:36, 130, 131 and 1023 and variants of primer/probe sequences under stringent conditions

The claims are open to any nucleic acid sequence, whether currently known or not. For this vast genus, only one species is provided. Thus, the conclusion is inescapable that the specification fails to provide a representative number of species in the genus of nucleic acid sequences that share any degree of homology or complementarity across the entire nucleic acid sequence of SEQ ID NO:36, 130, 131 and 1023, or nucleic acids which comprise 'a complement thereof' of nucleic acids which represent allelic variants of SEQ ID NO:36, 130, 131 and 1023.

Conclusion

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acid sequences other than those expressly disclosed which comprise the genus encompassed by nucleic acids comprising at least one CpG dinucleotide

sequence, complements of nucleic acids, or sequences with any degree of complementarity to SEQ ID NO:36, 130, 131 and 1023. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 14-18 and 27-37 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Distler et al. (WO02/103042; December 2002). Distler teaches the detection of prostate cancer using methylation changes in an array format (Abstract).

With regard to claim 1, Distler teaches a method for the detection of and/or differentiation between prostate cell proliferative disorders in a subject, comprising contacting genomic DNA isolated from a biological sample obtained from the subject, with at least one reagent, or series of reagents that distinguishes between methylated and non-methylated CpG dinucleotides within one or a combination of target nucleic acids (Abstract; Example 2, where prostate cancer was differentiated based on the analysis of methylation status of CpG dinucleotides in multiple genes using a set of primers as recited in Table 1), each of said target nucleic acids comprising essentially of all or part of the sequence of a gene or a genomic

sequence taken from the group consisting of SEQ ID NO:1023 and HISTONE H4, respectively, wherein said contiguous nucleotides comprise at least one CpG dinucleotide sequence, and whereby the detection of and/or differentiation between prostate cell proliferative disorders is, at least in part, afforded (Abstract; Example 2, where prostate cancer was differentiated based on the analysis of methylation status of CpG dinucleotides in multiple genes using a set of primers as recited in Table 1, where samples obtained from patients with benign hyperplasia were compared to patients with prostate carcinoma).

With regard to claim 2, Distler teaches a method for the detection of and/or differentiation between prostate cell proliferative disorders in a subject, comprising contacting genomic DNA isolated from a biological sample obtained from the subject, with at least one reagent, or series of reagents that distinguishes between methylated and non-methylated CpG dinucleotides within the target nucleic acid SEQ ID NO: 1023 wherein said contiguous nucleotides comprise at least one CpG dinucleotide sequence, and whereby the detection of and/or differentiation between prostate cell proliferative disorders is, at least in part, afforded (Abstract; Example 2, where prostate cancer was differentiated based on the analysis of methylation status of CpG dinucleotides in multiple genes using a set of primers as recited in Table 1, where samples obtained from patients with benign hyperplasia were compared to patients with prostate carcinoma and where any of the CpG dinucleotides detected read on the claim as currently broadly recited – see claim interpretation above).

With regard to claim 3, Distler teaches an embodiment of claim 7, comprising contacting genomic DNA isolated from a biological sample obtained from the subject, with at least one reagent, or series of reagents that distinguishes between methylated and non-methylated CpG

dinucleotides within one or more of target nucleic acids, each of said target nucleic acids comprising essentially of all or part of the sequence of a gene or a genomic sequence taken from the group consisting of HISTONE H4 (Abstract; Example 2, where prostate cancer was differentiated based on the analysis of methylation status of CpG dinucleotides in multiple genes using a set of primers as recited in Table 1, where samples obtained from patients with benign hyperplasia were compared to patients with prostate carcinoma and where the CpG dinucleotides detected read on the claim as currently recited – see claim interpretation above).

With regard to claim 4, Distler teaches an embodiment of claims 1 and 2, wherein prostate cancer, prostate carcinoma or prostate neoplasm is detected or distinguished (Abstract; Example 2, where prostate cancer was differentiated based on the analysis of methylation status of CpG dinucleotides in multiple genes using a set of primers as recited in Table 1, where samples obtained from patients with benign hyperplasia were compared to patients with prostate carcinoma).

With regard to claim 14, Distler teaches a method for detecting, or detecting and distinguishing between or among prostate cell proliferative disorders in a subject, comprising:

- a. obtaining, from a subject, a biological sample having subject genomic DNA; b. extracting or otherwise isolating the genomic DNA (p. 8, where in the first step, genomic DNA is isolated);
- c. treating the genomic DNA of b), or a fragment thereof, with one or more reagents to convert cytosine bases that are unmethylated in the 5-position thereof to uracil or to another base that is detectably dissimilar to cytosine in terms of hybridization properties (p. 2-3, where bisulfite treatment and conversion is used to detect methylation at CpG dinucleotides; p. 8-9, where the samples are treated with bisulfite);

d. contacting the treated genomic DNA, or the treated fragment thereof, with an amplification enzyme and at least two primers comprising, in each case a contiguous sequence of at least 9 nucleotides that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131 and complements thereof, wherein the treated genomic DNA or the fragment thereof is either amplified to produce at least one amplificate, or is not amplified (p. 9, where after treatment, the samples were treated with primers for amplification and where any sequence taught by Distler reads on “complements thereof” of SEQ ID NO:130 and 131); and

e. determining, based on a presence or absence of, or on a property of said amplificate, the methylation state of at least one CpG dinucleotide of a sequence selected from the group consisting SEQ ID NO: 1023, SEQ ID NO: 36 or an average, or a value reflecting an average methylation state of a plurality of CpG dinucleotides of a sequence selected from the groups consisting of SEQ ID NO: 1023, SEQ ID NO: 36, whereby at least one of detecting, or detecting and distinguishing between prostate cell proliferative disorders is, at least in part, afforded (p. 9-10, where the amplicates are hybridized to an array for detection and where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated and where any of the CpG dinucleotides detected read on the claim as currently broadly recited – see claim interpretation above).

With regard to claim 15, Distler teaches an embodiment of claim 14, wherein treating the genomic DNA, or the fragment thereof in c), comprises use of a reagent selected from the group consisting of bisulfite, hydrogen sulfite, disulfite, and combinations thereof (p. 2-3, where

bisulfite treatment and conversion is used to detect methylation at CpG dinucleotides; p. 8-9, where the samples are treated with bisulfite).

With regard to claim 16, Distler teaches an embodiment of claim 14, wherein contacting or amplifying in d) comprises use of at least one method selected from the group consisting of: use of a heat-resistant DNA polymerase as the amplification enzyme; use of a polymerase lacking 5'-3' exonuclease activity; use of a polymerase chain reaction (PCR); generation of a amplificate nucleic acid molecule carrying a detectable labels; and combinations thereof (p. 9, where the samples are amplified by PCR).

With regard to claim 17, Distler teaches an embodiment of claim 16, wherein the detectable amplificate label is selected from the label group consisting of: fluorescent labels; radionuclides or radiolabels; amplificate mass labels detectable in a mass spectrometer; detachable amplificate fragment mass labels detectable in a mass spectrometer; amplificate, and detachable amplificate fragment mass labels having a single-positive or single-negative net charge detectable in a mass spectrometer; and combinations thereof (p. 4-5, where mass spectrometry detection of methylation status of CpG dinucleotides is discussed).

With regard to claim 18, Distler teaches an embodiment of claim 14, wherein the biological sample obtained from the subject is selected from the group consisting of cell lines, histological slides, biopsies, paraffin- embedded tissue, bodily fluids, ejaculate, urine, blood, and combinations thereof (p. 8, where the biological samples are obtained from cell lines, biological slides, biopsies and other sample types).

With regard to claim 27, Distler teaches an embodiment of claim 14, wherein determining in e), comprises sequencing of the amplificate (Example 2, where individual CpG dinucleotides can be identified by sequencing).

With regard to claim 28, Distler teaches an embodiment of claim 14, wherein contacting or amplifying in d), comprises use of methylation-specific primers (p. 9, where the samples are amplified by PCR).

With regard to claim 29, Distler teaches an embodiment of claim 14 comprising in d) using primer oligonucleotides comprising one or more CpG; TpG or CpA dinucleotides; and further comprising in e) the use of at least one method selected from the group consisting of: hybridizing in at least one nucleic acid molecule or peptide nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131 and complements thereof (p. 7, where PNA probes are used for detection; p. 9-10, where the amplicates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ ID NO:130 and 131);

hybridizing at least one nucleic acid molecule that is bound to a solid phase and comprises a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131 and complements thereof (p. 9-10, where the amplicates are hybridized to an array for detection and where mass spectrometric detection is

preferred; see Example 2, where prostate cancer is differentiated and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ ID NO:130 and 131); hybridizing at least one nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131, and complements thereof, and extending at least one such hybridized nucleic acid molecule by at least one nucleotide base (p. 7, where PNA probes are used for detection; p. 9-10, where the amplicates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ ID NO:130 and 131); and sequencing in e) of the amplicate (Example 2, where individual CpG dinucleotides can be identified by sequencing).

With regard to claim 30, Distler teaches an embodiment of claim 14 comprising in d) use of at least one nucleic acid molecule or peptide nucleic acid molecule comprising in each case a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131 and complements thereof, wherein said nucleic acid molecule or peptide nucleic acid molecule suppresses amplification of the nucleic acid to which it is hybridized (p. 7, where PNA probes are used for detection; p. 9-10, where the amplicates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ

ID NO:130 and 131); and further comprising in e) the use of at least one method selected from the group consisting of: hybridizing in at least one nucleic acid molecule or peptide nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131 and complements thereof; hybridizing at least one nucleic acid molecule that is bound to a solid phase and comprises a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131 and complements thereof (p. 7, where PNA probes are used for detection; p. 9-10, where the amplicates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ ID NO:130 and 131); hybridizing at least one nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131, and complements thereof, and extending at least one such hybridized nucleic acid molecule by at least one nucleotide base (p. 9-10, where the amplicates are hybridized to an array for detection and where mass spectrometric detection is preferred and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ ID NO:130 and 131); and sequencing in e)

of the amplificate (Example 2, where individual CpG dinucleotides can be identified by sequencing).

With regard to claim 31, Distler teaches an embodiment of claim 14, comprising in d) amplification by primer oligonucleotides comprising one or more CpG; TpG or CpA dinucleotides (p. 9, where after treatment, the samples were treated with primers for amplification) and further comprising in e) hybridizing at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131 (p. 9-10, where the amplificates are hybridized to an array for detection and where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated).

With regard to claim 32, Distler teaches an embodiment of claim 14, comprising in d) the use of at least one nucleic acid molecule or peptide nucleic acid molecule comprising in each case a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NO: 130, 131 and complements thereof, wherein said nucleic acid molecule or peptide nucleic acid molecule suppresses amplification of the nucleic acid to which it is hybridized, and further comprising in e) hybridizing at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of 130, 131 (p. 7, where PNA probes are used for detection; p. 9-10, where the amplificates are hybridized to an array for detection and where the probes can

comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ ID NO:130 and 131).

With regard to claim 33, Distler teaches a method for detecting and/or distinguishing between or among prostate cell proliferative disorders in a subject, comprising: a. obtaining, from a subject, a biological sample having subject genomic DNA; b. extracting, or otherwise isolating the genomic DNA (p. 8, where in the first step, genomic DNA is isolated); e. contacting the genomic DNA of b), or a fragment thereof, comprising at least 16 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO:1023, SEQ ID NO: 36 and sequences that hybridize under stringent conditions thereto (see alignment above, where SEQ ID NO:29230 of Olek teaches complementarity to SEQ ID NO:1023), with one or more methylation-sensitive restriction enzymes, wherein the genomic DNA is, with respect to each cleavage recognition motif thereof, either cleaved thereby to produce cleavage fragments, or not cleaved thereby (p. 9, where after treatment, the samples were treated with primers for amplification;); and

d. determining, based on a presence or absence of, or on property of at least one such cleavage fragment, the methylation state of at least one CpG dinucleotide of a sequence selected from the group consisting of SEQ ID NO: 1023, SEQ ID NO: 36 (see alignment above, where SEQ ID NO:29230 of Olek teaches complementarity to SEQ ID NO:1023) or an average, or a value reflecting an average methylation state of a plurality of CpG dinucleotides of a sequence selected from the group consisting of SEQ ID NO: 1023, SEQ ID NO: 36, whereby at least one of detecting, or of detecting and differentiating between or among prostate cell proliferative

disorders is, at least in part, afforded (p. 9-10, where the amplicates are hybridized to an array for detection and where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated).

With regard to claim 34, Distler teaches an embodiment of claim 33, further comprising, prior to determining in d), amplifying of the digested or undigested genomic DNA (p. 9, where after treatment, the samples were treated with primers for amplification).

With regard to claim 35, Distler teaches an embodiment of claim 34, wherein amplifying comprises use of at least one method selected from the group consisting of: use of a heat resistant DNA polymerase as an amplification enzyme; use of a polymerase lacking 5'-3' exonuclease activity; use of a polymerase chain reaction (PCR); generation of a amplicate nucleic acid carrying a detectable label; and combinations thereof (p. 9, where the samples are amplified by PCR).

With regard to claim 36, Distler teaches an embodiment of claim 35, wherein the detectable amplicate label is selected from the label group consisting of: fluorescent labels; radionuclides or radiolabels; amplicate mass labels detectable in a mass spectrometer; detachable amplicate fragment mass labels detectable in a mass spectrometer; amplicate, and detachable amplicate fragment mass labels having a single-positive or single-negative net charge detectable in a mass spectrometer; and combinations thereof (p. 4-5, where mass spectrometry detection of methylation status of CpG dinucleotides is discussed; p. 9-10, where the amplicates are hybridized to an array for detection and where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated).

With regard to claim 37, Distler teaches an embodiment of claim 33, wherein the biological sample obtained from the subject is selected from the group consisting of cell lines, histological slides, biopsies, paraffin- embedded tissue, bodily fluids, ejaculate, urine, blood, and combinations thereof (p. 8, where the biological samples are obtained from cell lines, biological slides, biopsies and other sample types).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-10 and 29-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Distler et al. (WO02/103042; December 2002) as applied to claims 1-4, 14-18 and 27-37 above and further in view of Wang et al. (US Patent H002220; July 2008) and Buck et al.

(Biotechniques, 1999, 27, p. 528-536. Distler teaches the detection of prostate cancer using methylation changes in an array format (Abstract).

With regard to claim 5, Distler teaches a method for detecting and/or distinguishing between or among prostate cell proliferative disorders in a subject, comprising:

- obtaining, from a subject, a biological sample having subject genomic DNA (p. 8, where in the first step, genomic DNA is isolated);
- contacting the genomic DNA, or a fragment thereof, with one reagent or a plurality of reagents for distinguishing between methylated and non methylated CpG dinucleotide sequences within at least one target sequence of the genomic DNA, or fragment thereof, wherein the target sequence comprises, or hybridizes under stringent conditions said contiguous nucleotides comprising at least one CpG dinucleotide sequence (p. 9, where after treatment, the samples were treated with primers for amplification)

- determining, based at least in part on said distinguishing, the methylation state of at least one target CpG dinucleotide sequence, or an average, or a value reflecting an average methylation state of a plurality of target CpG dinucleotide sequences, whereby detecting, or detecting and distinguishing between or among prostate cell proliferative disorders is, at least in part, afforded (p. 9-10, where the amplicates are hybridized to an array for detection and where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated based on the analysis of methylation status of CpG dinucleotides in multiple genes using a set of primers as recited in Table 1, where samples obtained from patients with benign hyperplasia were compared to patients with prostate carcinoma).

With regard to claim 6, Distler teaches an embodiment of claim 5, wherein distinguishing between methylated and non methylated CpG dinucleotide sequences within the target sequence comprises converting unmethylated cytosine bases within the target sequence to uracil or to another base that is detectably dissimilar to cytosine in terms of hybridization properties (p. 2-3, where bisulfite treatment and conversion is used to detect methylation at CpG dinucleotides; p. 8-9, where the samples are treated with bisulfite).

With regard to claim 7, Distler teaches an embodiment of claim 5, wherein distinguishing between methylated and non methylated CpG dinucleotide sequences within the target sequence(s) comprises methylation state-dependent conversion or non-conversion of at least one CpG dinucleotide sequence to the corresponding converted or non-converted dinucleotide sequence (p. 2-3, where bisulfite treatment and conversion is used to detect methylation at CpG dinucleotides; p. 8-9, where the samples are treated with bisulfite).

With regard to claim 8, Distler teaches an embodiment of claim 5, wherein the biological sample is selected from the group consisting of cell lines, histological slides, biopsies, paraffin-embedded tissue, bodily fluids, ejaculate, urine, blood, and combinations thereof (p. 8, where the biological samples are obtained from cell lines, biological slides, biopsies and other sample types).

With regard to claim 9, Distler teaches an embodiment of claim 5, wherein distinguishing between methylated and non methylated CpG dinucleotide sequences within the target sequence comprises use of at least one nucleic acid molecule or peptide nucleic acid (PNA) molecule comprising, in each case a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence

(p. 7, where PNA probes are used for detection; p. 9-10, where the amplicates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated).

With regard to claim 10, Distler teaches an embodiment of claim 9, wherein the contiguous sequence comprises at least one CpG, TpG or CpA dinucleotide sequence (Abstract; Example 2, where prostate cancer was differentiated based on the analysis of methylation status of CpG dinucleotides in multiple genes using a set of primers as recited in Table 1, where samples obtained from patients with benign hyperplasia were compared to patients with prostate carcinoma).

With regard to claim 29, Distler teaches an embodiment of claim 14 comprising in d) using primer oligonucleotides comprising one or more CpG; TpG or CpA dinucleotides; and further comprising in e) the use of at least one method selected from the group consisting of: hybridizing in at least one nucleic acid molecule or peptide nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence (p. 7, where PNA probes are used for detection; p. 9-10, where the amplicates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated);

hybridizing at least one nucleic acid molecule that is bound to a solid phase and comprises a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence and complements thereof (p. 9-10, where the amplicates are hybridized to an array for detection and where mass

spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated); hybridizing at least one nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of a sequence and complements thereof, and extending at least one such hybridized nucleic acid molecule by at least one nucleotide base; and sequencing in e) of the amplificate (Example 2, where individual CpG dinucleotides can be identified by sequencing).

With regard to claim 30, Distler teaches an embodiment of claim 14 comprising in d) use of at least one nucleic acid molecule or peptide nucleic acid molecule comprising in each case a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of a sequence and complements thereof, wherein said nucleic acid molecule or peptide nucleic acid molecule suppresses amplification of the nucleic acid to which it is hybridized (p. 7, where PNA probes are used for detection; p. 9-10, where the amplificates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ ID NO:130 and 131); and further comprising in e) the use of at least one method selected from the group consisting of: hybridizing in at least one nucleic acid molecule or peptide nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence and complements thereof;

hybridizing at least one nucleic acid molecule that is bound to a solid phase and comprises a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence and complements thereof (p. 7, where PNA probes are used for detection; p. 9-10, where the amplicates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated);

hybridizing at least one nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence complements thereof, and extending at least one such hybridized nucleic acid molecule by at least one nucleotide base (p. 9-10, where the amplicates are hybridized to an array for detection and where mass spectrometric detection is preferred); and sequencing in e) of the amplicate (Example 2, where individual CpG dinucleotides can be identified by sequencing).

With regard to claim 31, Distler teaches an embodiment of claim 14, comprising in d) amplification by primer oligonucleotides comprising one or more CpG; TpG or CpA dinucleotides (p. 9, where after treatment, the samples were treated with primers for amplification) and further comprising in e) hybridizing at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence (p. 9-10, where the amplicates are hybridized to an array for detection and where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated).

With regard to claim 32, Distler teaches an embodiment of claim 14, comprising in d) the use of at least one nucleic acid molecule or peptide nucleic acid molecule comprising in each case a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence and complements thereof, wherein said nucleic acid molecule or peptide nucleic acid molecule suppresses amplification of the nucleic acid to which it is hybridized, and further comprising in e) hybridizing at least one detectably labeled nucleic acid molecule comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence (p. 7, where PNA probes are used for detection; p. 9-10, where the amplicates are hybridized to an array for detection and where the probes can comprise PNA probes where mass spectrometric detection is preferred; see Example 2, where prostate cancer is differentiated and where any sequence of 2 consecutive nucleotides can read on a complement thereof of SEQ ID NO:130 and 131).

Regarding claim 5 and 33, Distler does not specifically teach at least 16 contiguous nucleotides of a sequence taken from the group consisting of SEQ ID NO: 1023, SEQ ID NO: 36. Regarding claim 7, 9, 29-32, Distler does not teach a sequence selected from the group consisting of SEQ ID NO:130, 131, and contiguous regions thereof corresponding to the target sequence.

With regard to claim 5, 14, 33, Wang teaches sequence hybridizes to at least 16 contiguous nucleotides of a sequence taken from the group consisting of SEQ ID NO: 1023, SEQ ID NO: 36 (see alignment below, where SEQ ID NO:865335 of Wang teaches complementarity to SEQ ID NO:1023).

Qy	176	GTGCCAGCCCTCTCCTGGTCTTGATTGTGTTTTGACAGCCGTGAGATGGTGTGTC	235
Db	521	GTGCCAGCCCTCTCCTGGTCTTGATTGTGTTTTGACAGCCGTGAGATGGTGTGTC	462
Qy	236	CCACTAAGTAATATGCCCTGTCACTACATCATACTTTGCAGTTGTTGGGATTCTACGTA	295
Db	461	CCACTAAGTAATATGCCCTGTCACTACATCATACTTTGCAGTTGTTGGGATTCTACGTA	402
Qy	296	AAAGCACTTCACCTTAATGCTGCCTTAATTTCCCTTATGGTACTATACTGGGGGAAAT	355
Db	401	AAAGCACTTCACCTTAATGCTGCCTTAATTTCCCTTATGGTACTATACTGGGGGAAAT	342
Qy	356	TTTTCTTATAAATAAGAATCCTGGTCCTGGGCATTCATAGATGGTATTTAATTACTTT	415
Db	341	TTTTCTTATAAATAAGAATCCTGGTCCTGGGCATTCATAGATGGTATTTAATTACTTT	282
Qy	416	TTCCAATGCCCTTGCAAAATAGATGCTTTTCCTCTTTTGCCAGCTGAGGAAATAAGGTT	475
Db	281	TTCCAATGCCCTTGCAAAATAGATGCTTTTCCTCTTTTGCCAGCTGAGGAAATAAGGTT	223
Qy	476	AGTATGGTTAAACAGTCGGCTCAGGCCACACAGCTAACGAGGGAGAAGTCAGGATTGAA	535
Db	222	AGTATGGTTAAACAGTCGGCTCAGGCCACACAGCTAACGAGGGAGAAGTCAGGATTGAA	163
Qy	536	CTCGAGTCTCATTTCAAACCCATCTTGTATCGCAGCAGAACCTTTACCTATTAAAGCT	595
Db	162	CTCSAGTCTCATTTCAAACCCATCTTGTATCGCAGCAGAACCTTTACCTATTAAAGCT	103
Qy	596	AAGGACGTTTAGATGGCTTTGTGCTTTTGCACTCATCTGAAAAATGTTTTAAAGTTG	655
Db	102	AAGGACGTTTAGATGGCTTTGTGCTTTTGCACTCATCTGAAAAATGTTTTAAAGTTG	43
Qy	656	GCAGATGAGTTCTAATTGTGGTTCCTCATTTTTTTCCTCATG	697
Db	42	GCAGATGAGTTCTAATTGTGGTTCCTCATTTTTTTCCTCATG	1

With regard to claim 7, 9, 29-32, Wang teaches a sequence comprising contiguous sequence at least 9 nucleotides in length selected from the group consisting of SEQ ID NO:130, 131, and contiguous regions thereof corresponding to the target sequence or a complement thereof (see alignment below, where SEQ ID NO:793719 of Wang comprises at least 9 contiguous nucleotides of SEQ ID NO:130 and SEQ ID NO:131).

SEQ ID NO:130

Qy	1	TTTGTAAATGGAGATATTTTTATTATTTTATAGTATTATATGTTTTTAAAGTTGTATT	60
Db	448	TTTGTAAATGGAGACATCTTCATTATTCCTATAGTATCATATGTTTTTAAAGTTGTACT	389
Qy	61	TATATTTTGGGTGATAAATGAAGATAAGATTTTTTTTATTTTGTGAGGATGATTATA	120

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Db	388	CACACTTTGGGTGATAAATGAAGGACAAGATCCTTCCCTATCCTTGTGAGGATGACTACA	329
Qy	121	GTATGATTGGATGGGTTTGTATGATTTTATTTTTTTTGTGTTTTTATTTATCGTTTTA	180
Db	328	GCATGACTGGATGGGCTTGCCTATGATTTTATCTTCCCTGTGTTCTCACTACCGTTTTA	269
Qy	181	TTAAATTTAGTTTTTTTTTATAGGGTAGTATAGAATTTAAATAGTAGAAAAGAGATTAGT	240
Db	268	TTAACTCAGTCTTTTTCACAGGGTAGCAGAGATTTAACTAGCAGAAAAGAGATCCAGC	209
Qy	241	TATGTAGATTAGAGATTTGTTTAAAGTGACGGTAGTGAAGAATTAGGAAGGAAAGTTTTT	300
Db	208	CATGTAGACCAGAGATTTGTCTAAGTGACGGCATGTAGAATCAGGAAGGAAAGTTTTT	149
Qy	301	GTTTAAATATTAATAGGTTTTTTTTTTAAAGTAATTATTATTTTTTAAATTTAATTATA	360
Db	148	GTTTAAATCAACAGGTCCTTCTCTTAAAGCAATTATTATTTTTTCAAATCAACCCACA	89
Qy	361	AGGTGATAGTATTTTTTAAATTAATTAATTAAGATTTTCGGGTTGGATAATTTTAAATATG	420
Db	88	AGGTGATAGTATCCTTAAACCAATTAATCAGAATCTCGGGTTGGATAACCTCAAATATG	29
Qy	421	ATTTATTAGTATTTTTTATTAATTAATTG 448	
Db	28	ACTTATTAGCACTCCCAATTAATCACTG 1	

SEO ID NO:131

Qy	1	AAAAAAATTTTTTTTTGATTATTTATATGCTGATTAATTAGATAAAATTTTGGTTTATATG	60
Db	149	AAAAAACTTCTCTCTGATCTTACATGCCGTCACTTTAGACAAATCTCTGGTCTACATG	208
Qy	61	GTTGGATTTTTTTTTGTTAGTTAAATTTTGTTGTTATTTTGTGAAAAAGAAATGAGATTAA	120
Db	209	GCTGATGATCTCTTCTGCTAGTTAAATTTCTGTGCTACCCCTGTGAAAAAGAACTGAGATTAA	268
Qy	121	TAAACCGTAGTGAGAATATAGGGAAGATAAAAAATATAGTAAGTTTATTAGTTATGT	180
Db	269	TAAACCGTAGTGAGAACAAGGGAAGATAAAATCATGCAAGCCCATCCAGTCATGC	328
Qy	181	TGTAGTTATTTTTATAAGGATAGGGAAGGATTTGTGTTTTTATTATTATTAAAGTGTG	240
Db	329	TGTAGTCATCTCCACAAGGATAGGGAAGGATCTGTGCTTCATTATCACCCCAAAGTGTG	388
Qy	241	AGTATAAAATTTAAAAATATATGATATTATAGGAATAATGAAGATGTTTTTATTGTAAA	300
Db	389	AGTACAAACCTTTAAAAACATATGTACTATAGGAATAATGAAGATGTCTCCATTTCGAAA	448

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Distler to include additional targets for the methylation analysis and to include primers for amplification as taught by Wang.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of prostate cancer related sequences, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are prima facie obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary

criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Primary Examiner, Art Unit 1637

SKM

